REMARKS

On pages 2-3 of the Office Action, the Examiner rejects Claims 2-7 and 9-10 under 35 U.S.C. § 112, second paragraph.

With respect to Claim 9, the Examiner states that the term "accessing" is confusing, since it does not set forth the manner in which the "anti-bacterial effects" are determined.

In view of the amendment to the preamble of Claim 9 to recite "A method for identifying whether a test compound has any anti-bacterial activity...", Applicants respectfully submit that the Examiner's rejection has been met.

Further, the Examiner states that the optional isolation step in Claim 9 is confusing.

The Examiner is requested to note the agent is actually a crude composition containing the test compound. Thus, in view of the amendments to Claim 9 to set forth such, Applicants respectfully submit that the Examiner's rejection has been met.

Further, with respect to Claim 9, the Examiner states that the extent of "exhibiting anti-bacterial activity" can not be ascertained.

The Examiner is requested to note that the invention relates to assaying any anti-bacterial activity. Thus, in view of the amendments to Claim 9 to set forth such, Applicants respectfully submit that the Examiner's rejection has been met.

Finally, with respect to Claim 9, the Examiner states that the claim does not specify how the selection of a phenotypically antibiotic-resistant subpopulation is to be effected; i.e., the Examiner states that there is no indication of the concentration of antibiotic or the nature of the concentration of the bacteria

to be treated to obtain the resistant subpopulation. The Examiner states that the assessment of the effects on a mixture of antibiotics would not be expected to be readily achievable.

The Examiner is requested to note that a single strain is cultured in the present invention, not a mixed culture. Thus, in view of the amendments to Claim 9 to set forth that "an antibiotic-sensitive strain" is grown in step (a), Applicants respectfully submit that the Examiner's rejection has been met.

The Examiner is also requested to note that the concentration of antibiotic employed will depend upon the bacteria strain employed, and that such can be readily determined by one skilled in the art. Thus, Applicants respectfully traverse the Examiner's rejection with respect to the antibiotic concentration. Further, the particular antibiotic employed is not critical to the present invention. Thus, Applicants respectfully traverse the Examiner's rejection with respect to this aspect of the Examiner's rejection.

As to Claim 10, the Examiner states that Claim 10 does not have antecedent basis in Claim 9 for the "identified agent or compound", as there is no identification step in Claim 9.

In view of the amendment to Claim 9 to include an identifying step, Applicants respectfully submit that the Examiner's rejection has been met.

Further, the Examiner states that Claim 10 is confusing in recitation of the "step of amplifying".

"Amplification" in Claim 10 is to be taken as meaning the maximization of the production of the compound of interest

(noted by the Examiner to be defined as such in Shomura (U.S. Patent 3,697,648), e.g., Examples 1 and 2).

With respect to Claim 3, the Examiner states that such is confusing in lacking antecedent basis, i.e., the Examiner asks whether the concentration required is to produce the resistant population or the concentration tested.

The Examiner is requested to note that the concentrations of antibiotic and bacteria referred to in Claim 3 are for the antibiotic and bacteria of step (b) of Claim 9. Thus, in view of the amendments to Claim 3 to clearly set forth such, Applicants respectfully submit that the Examiner's rejection has been met.

As to Claims 5-7, the Examiner contends that these claims are confusing in that the antecedent basis in Claim 9 for said "said antibiotic" is uncertain.

The Examiner is requested to note that the antibiotic is that referred to in step (b). Thus, in view of the amendments to Claims 5-7 to clearly set forth such, Applicants respectfully submit that the Examiner's rejection has been met.

Further, the Examiner states that strains of *E. coli*, *S. aureus* and *M. tuberculosis*, which are resistant to kanamycin, ampicillin and rifampicin are known in the art.

In view of the amendments to amend step (a) to set forth that the strain is an "antibiotic-sensitive" bacterial strain, Applicants respectfully submit that the Examiner's rejection has been met.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

On page 3 of the Office Action, the Examiner rejects Claims 2-4, 6-7 and 9-10 under 35 U.S.C. § 103 as being unpatentable over Sahm et al, in view of Pelczar, George et al, Shomura et al and Barth.

Specifically, the Examiner states that Sahm et al discloses a process for assessing antibiotic susceptibility of resistant bacteria, wherein the resistant bacteria were tested with various antibiotics.

The Examiner notes that Sahm et al is different from the present invention in that the selection of resistant bacteria from stationary cultures is not disclosed. However, the Examiner contends that selecting for bacteria resistant to antibiotics is known, as demonstrated by Pelczar, and that George et al discloses a process for obtaining resistant bacteria cells where the cells are grown to stationary phase.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The Examiner appears to have missed a fundamental inventive concept of the present invention when analyzing the prior art. The prior art is concerned with targeting bacteria that are genetically resistant to anti-bacterial agents. This approach is only effective against bacteria multiplying at the time of exposure to the anti-bacterial agent (see page 1, line 34 to page 2, line 13 of the present application).

On the other hand, the present invention is concerned with phenotypic resistance (tolerance) of bacteria to anti-bacterial agents and provides a strategy of targeting non-multiplying latent (stationary phase) bacteria (see page 3, lines 4 to 18 of the present application). The stationary phase bacteria are a cause of increased length of infection, as they are able to tolerate repeated doses of anti-bacterial agents. Stationary phase bacteria are able to become actively multiplying bacteria again, thereby prolonging the course of infection and increasing the length of treatment required (see page 4, line 34 to page 5, line 1 of the present application).

Bacteria can possess two types of resistance, phenotypic and genetic. Phenotypic resistance is the tolerance of anti-bacterial agents, usually during the stationary phase. Phenotypic resistance is only temporary, as the bacteria become sensitive to the anti-bacterial agent when they resume multiplying.

Genetic resistance occurs when a gene mutates and so confers resistance to a particular anti-bacterial agent, i.e., a permanent resistance. Some incidences of genetic resistance arise during a period of phenotypic resistance and in particular when the bacteria are latent for long periods of time. In other words, phenotypic resistance is often a step on the way to the development of genetic resistance.

The present invention is directed to identifying compounds that reduce and/or eliminate the stationary phase bacteria (exhibiting phenotypic resistance) in order to prevent further "waves" of active multiplying bacteria. These compounds both

shorten the treatment time and reduce the number of phenotypically resistance bacteria available to give rise to genetically resistance bacteria, and consequently reduce the number of permanently resistant bacteria.

Anti-bacterial activity against stationary phase bacteria is a completely new and non-obvious concept in the treatment of bacterial infections. The references cited by the Examiner are only relevant to compounds and methods specific to genetically resistant bacteria. Targeting stationary phase bacteria, as claimed in the present application, has neither been attempted nor suggested, in any of the cited references, and therefore the skilled person would not have considered it obvious to target phenotypic resistance as a method of shortening treatment times and/or reducing the genetically resistant bacterial population.

An important review article on treating bacterial infection by Applicants has recently been published in Nature Review Drug Discovery, 1(11):895-910 (November 2002) (a copy of which is attached hereto). This review article includes an extensive discussion of all aspects of resistance to anti-bacterial resistance, including a section on phenotypic resistance and how prior art methods of bacterial treatment do not address the problem of phenotypic resistance (see page 903, column 1, last paragraph *et seq*).

Turning now to the cited references.

Sahm et al discloses studies of vancomycin resistant *Enterrococcus faecilis* that are susceptible to teicoplanin. However, no mention is made therein of the selection of

resistant bacteria from stationary cultures, as claimed in the present application.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Sahm et al, and for the following reasons, it is clear that Pleczar, George et al, Shomura et al and Barth do not provide the deficiencies that exist therein.

Pelczar et al discloses a method of selecting resistant bacteria. However, no mention is made therein of growth to the stationary phase, nor that the bacteria are phenotypically resistant, as claimed in the present application.

George et al discloses growth of bacteria to stationary phase to select those exhibiting resistance. However, the bacteria thereof are not selected for further use in relation to identifying anti-bacterial agents effective against resistant stationary phase bacteria, nor is any indication provided of the possibility of investigating these bacteria further.

Furthermore, George et al is directed to investigating the source of the genetic resistance of these resistant bacteria, and makes no mention of phenotypic resistance, as claimed in the present application. It is not essential, for the study of genetic resistance, to grow the bacteria to stationary phase, whereas, the phenotypic anti-bacterial resistance being targeted in the present invention, only occurs during the stationary phase.

Shomura et al is concerned with the testing of antibiotics on kanamycin resistant bacteria, whilst Barth et al concerns the testing of antibiotics on ampicillin resistant bacteria.

Neither of these references teach or suggest growth to stationary phase or phenotypic resistant bacteria investigations, as claimed in the present application.

Thus, Sahm et al, when considered in combination with any of Pelczar, George et al, Shomura et al and Barth, does not teach or suggest the possibility of growing bacteria to stationary phase in order to provide pharmaceutical compositions that are effective against phenotypic resistance, as claimed in the present specification.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Sahm et al, alone or when combined with the teachings of Pleczar, George et al, Shomura et al and Barth, and in any event, the combination thereof can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

On page 5 of the Office Action, the Examiner rejects Claim 5 under 35 U.S.C. § 103 as being unpatentable over Sahm et al in view of Pelczar, Shomura et al and Barth, and further in view of Murray et al and the Merck Index.

Specifically, the Examiner states that Murray et al discloses that rifampicin resistant strains are known in the art, and the Merck Index discloses that the rifampin and rifampicin are the same.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, the present invention is not taught or suggested in Sahm et al, alone or when combined with the

teachings of Pleczar, George et al, Shomura et al and Barth. Further, it is clear that Murray et al and the Merck Index do not provide the deficiencies that exist therein.

The Examiner is requested to note that Claim 5 is dependent upon Claim 9. Thus, since, as discussed above, the Examiner's rejection of Claim 9 is improper, this rejection is also improper.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Sahm et al, alone or when combined with the teachings of Pleczar, George et al, Shomura et al, Barth, Murray et al and the Merck Index, and in any event, the combination thereof can only be made in hindsight, which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration, and allowance are requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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APPENDIX

Marked-up Version of Changes

IN THE CLAIMS:

The claims are amended as follows:

Claim 2. (Twice Amended) The method as claimed in Claim 9, wherein said antibiotic in step (b) is selected from the group consisting of rifampicin, kanamycin, ampicillin and pyrazinamide.

Claim 3. (Thrice Amended) The method as claimed in Claim 9, wherein in step (b) said concentration of said at least one antibiotic is [used at a concentration of] 25 to 150 µg/ml and [with] said stationary phase culture contain [bacteria present at a concentration of] 10^5 to 10^9 bacteria/ml.

Claim 4. (Thrice Amended) The method as claimed in Claim 9, wherein said bacteria strain is [are] selected from the group consisting of *Staphylococcus aureus*, *Escherichia coli*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus gordonii* and *Mycobacterium tuberculosis*.

Claim 5. (Thrice Amended) The method as claimed in Claim 9, wherein said bacteria strain is [are] *Mycobacterium tuberculosis* and said antibiotic in step (b) is rifampicin.

Claim 6. (Thrice Amended) The method as claimed in Claim 9, wherein said bacteria strain is [are] *Escherichia coli* and said antibiotic in step (b) is kanamycin.

Claim 7. (Thrice Amended) The method as claimed in Claim 9, wherein said bacteria strain is [are] *Staphylococcus aureus* and said antibiotic in step (b) is ampicillin.

Claim 9. (Thrice Amended) A method for [assessing the antibacterial activity of] identifying whether a test compound [or agent or for isolating a compound or agent having] has any antibacterial activity against stationary phase bacteria comprising the steps of:

(i) preparing a phenotypically antibiotic-resistant subpopulation of stationary phase bacteria according to the method comprising at least the steps of:

(a) growing [a] an antibiotic-sensitive bacterial [culture] strain to stationary phase to obtain a stationary phase culture; and

(b) treating the resulting stationary phase culture with at least one antibiotic at a concentration and for a time sufficient to kill growing bacteria of said strain, and selecting a phenotypically antibiotic-resistant subpopulation;

(ii) incubating a sample of said phenotypically antibiotic resistant subpopulation with [at least one] said test compound or a composition comprising said test compound [or agent]; and

(iii) [assessing any] assaying whether said test compound or composition exhibits any antibacterial [effects] activity against said phenotypically antibiotic-resistant subpopulation so as to identify whether said test compound test compound or composition has any antibacterial activity against said stationary phase bacteria; and optionally

(iv) isolating [a] said test compound [or agent exhibiting antibacterial activity] from said composition.

Claim 10. (Twice Amended) The method according to Claim 9, further comprising the step of amplifying [the identified agent or] said test compound.